Intramural papers of the month

By Kimberly Cannady, Kristin Lichti-Kaiser, Zachary McCaw, and Staton Wade

Risk factor for lung disease in premature infants

NIEHS scientists and their colleagues have identified a gene known as Chrm2 that may make premature infants susceptible to a chronic lung disease called bronchopulmonary dysplasia (BPD).

Following up on previous studies that unveiled a genetic component to BPD, researchers exposed neonatal mice to either supplemental oxygen or room air (control group). The mice that were exposed to supplemental oxygen sustained more lung inflammation than the control group, but the severity of the damage varied depending on the genetic background of each mouse. Using a statistical technique called genome-wide association mapping, researchers identified chromosomal regions containing genetic sequence differences that could account for the differential responses.

Chrm2 was among the candidate genes identified. They found that mice with a functional mutation in the Chrm2 gene, which codes for receptors that contribute to a certain type of airway inflammation, experienced less lung injury and inflammation. Because this damage is similar to the respiratory injury seen in human BPD, the researchers may be able to use Chrm2 both as a therapeutic target to prevent neonatal lung injury and as a way to identify individuals at risk of developing BPD. **(ZM)**

Citation: Nichols JL, Gladwell W, Verhein KC, Cho HY, Wess J, Suzuki O, Wiltshire T, Kleeberger SR. *(http://www.ncbi.nlm.nih.gov/pubmed/24571919)*
2014. Genome-wide associated mapping of acute lung injury in neonatal inbred mice. FASEB J; doi:10.1096/fj.13-247221 [Online 26 February 2014].

A fresh look at the genetics of breast cancer

Analyzing data from the NIEHS Sister Study, NIEHS scientists have found evidence suggesting that breast cancer risk is influenced by nonstandard genetic mechanisms. The Sister Study *(http://sisterstudy.niehs.nih.gov/)* is a cohort of more than 50,000 sisters of women who have had breast cancer. The study, published in the journal PLOS Genetics, is the first to broadly assess possible contributions of understudied genetic mechanisms to the risk of breast cancer.

Genome-wide association studies have largely overlooked certain genetic mechanisms. For example, the maternal genome can act prenatally, the effect of a gene variant can depend on the parent of origin, and mitochondrial variants can influence risk. Because these mechanisms produce asymmetry in family histories of breast cancer, the scientists analyzed Sister Study data to compare rates in maternal versus paternal grandmothers. Significantly more maternal grandmothers than paternal grandmothers had developed breast cancer.

Using algebraic formulae, the researchers quantified the contributions of the nonstandard mechanisms to the asymmetry and showed that the small difference observed between maternal and paternal lineages could arise from a single nonstandard mechanism with a large effect. Ongoing analyses using families in the Two Sister Study, *(http://www.sisterstudy.niehs.nih.gov/English/2sis.htm)* an offshoot of the Sister Study, may be able to pinpoint the nonstandard mechanisms more directly. **(KC)**

Citation: Weinberg CR, Shi M, Deroo LA, Taylor JA, Sandler DP, Umbach DM. *(http://www.ncbi.nlm.nih.gov/pubmed/24651610)*
2014. Asymmetry in family history implicates nonstandard genetic mechanisms: application to the genetics of breast cancer. PLoS Genet 10(3):e1004174.

Humans with APOE4 gene more prone to inflammation

NIEHS scientists and their colleagues are the first to report that people with a particular form of the lipid-regulating gene apolipoprotein E (APOE) - specifically the APOE4 allele - may be more prone to inflammation than others. Their findings were

published in the Journal of Allergy and Clinical Immunology.

The researchers used the NIEHS Environmental Polymorphisms Registry *(http://dnaregistry.niehs.nih.gov/)* to identify healthy volunteers, based on their APOE genotype. Using the NIEHS Clinical Research Unit to obtain and examine the samples, they found that whole blood from patients with at least one copy of APOE4 produced a more robust inflammatory response to lipopolysaccharide (LPS), a surface component of bacteria, than blood from patients who didn't express APOE4. Intravenous injection of LPS into another group of volunteers showed that those with APOE4 had a higher fever and inflammatory response than those without APOE4. Similarly, mice genetically engineered to express human APOE4 were injected with LPS and exhibited an enhanced inflammatory response. Finally, the researchers also found that APOE4 was associated with increased illness severity and coagulation system failure in patients with sepsis, a dysregulated innate immune response to infection.

APOE4 has been previously associated with the development of inflammatory diseases, such as cardiovascular disease and Alzheimer's. These findings indicate that APOE4 may contribute to the inflammatory disease process through its regulation of the innate immune response. **(KLK)**

Citation: Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray Dudenkov T, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB. *(http://www.ncbi.nlm.nih.gov/pubmed/24655576)* 2014. APOepsilon4 is associated with enhanced in vivo innate immune responses in human subjects. J Allergy Clin Immunol; doi:10.1016/j/jaci.2014.01.032 [Online 18 March 2014]. [Story]

Regulation of alternative polyadenylation is required for ESC self-renewal

NIEHS researchers and their collaborators have described a novel regulatory mechanism that explains how cells choose between multiple sites at the end of a gene for transcriptional termination, a process known as alternative polyadenylation (APA). APA is known to occur during development and carcinogenesis, and in response to environmental factors. However, this work provides the first evidence that APA regulation is critical for embryonic stem cell (ESC) self-renewal and cell fate decisions.

The scientists discovered that Fip1, a 3' mRNA processing factor, is required for ESC self-renewal and somatic cell reprogramming. Direct RNA sequencing, a technique that maps polyadenylation sites (PASs) at the 3' end of transcripts, demonstrated that Fip1 depletion alters the APA profiles of 374 genes in ESCs. Furthermore, Fip1 depletion resulted in transcripts with longer 3' untranslated regions and repressed the protein expression of many genes involved in self-renewal.

Mechanistically, the authors demonstrated that high levels of Fip1 in ESCs promote the usage of weaker, gene-proximal PASs, and that this effect is dependent on the distance between the alternative PASs of a given gene. Conversely, Fip1 repression during differentiation promotes distal PAS usage. The authors speculate that similar mechanisms may regulate APA changes during oncogenesis and embryonic development. **(SW)**

Citation: Lackford B, Yao C, Charles GM, Weng L, Zheng X, Choi EA, Xie X, Wan J, Xing Y, Freudenberg JM, Yang P, Jothi R, Hu G, Shi Y. *(http://www.ncbi.nlm.nih.gov/pubmed/24596251)* 2014. Fip1 regulates mRNA alternative polyadenylation to promote stem cell self-renewal. EMBO J 33(8):878-889.

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